Abstract
Therapeutic resistance is the major cause for a poor prognosis in cancer patients. Clinical results of anti-angiogenic therapies are very modest, resulting in a moderate improvement of overall survival, and the clinical outcome is associated with the development of resistance. The clinical benefit of anti-angiogenic drugs is due to several intrinsic and acquired limitations including tumor indifference to anti-angiogenic therapy; selection of resistant clones and activation of alternative mechanisms that lead to activation of angiogenesis, even when the target of the drug remains inhibited; therapy-induced reduction of oxygen levels within the tumor and accumulation of infiltrating cancer stem cells; activation of pro-invasive mechanisms and increased dissemination and metastasis; normalization of tumor blood vessels; recruitment of inflammatory cells and immature myeloid cells; alternative mechanisms of tumor vessel formation; and genomic instability of tumor endothelial cells. In this context, the concept and strategies of anti-angiogenic therapies should be extensively reconsidered and reevaluated. In particular, rational combinations of anti-angiogenic agents based on pharmacokinetic and pharmacodynamics data are needed to overcome resistance.

Keywords
Angiogenesis • Anti-Angiogenesis • Resistance • Tumor Growth • VEGF

Contents
Introduction ............................................ 2
Anti-Angiogenesis ..................................... 2
Development of Resistance ......................... 3
Normalization of Tumor Blood Vessels and Pericyte Coverage ......................... 3
Hypoxia .................................................. 4
Recruitment of Inflammatory Cells and Immature Myeloid Cells ....................... 5
Alternative Mechanisms of Tumor Vessel Formation ..................................... 5
Genomic Instability of Tumor Endothelial Cells and Increase of Metastatic Potential ............. 6
Conclusion ................................................ 7
Cross-References ....................................... 8
References ............................................... 8

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Introduction

In 1971, Judah Folkman first advanced the hypothesis that tumor growth also depends on the formation of new blood vessels from the pre-existing vascular bed (Folkman 1971). It is now generally accepted that tumor growth is angiogenesis dependent and that any increment of tumor growth requires an increase in vascular growth (Ribatti et al. 1999). Most human tumors arise and remain in situ without angiogenesis for a long time before they switch to an angiogenic phenotype (Ribatti et al. 2007a). Dormant tumors have been discovered during autopsies of individuals who died of causes other than cancer (Black and Welch 1993). Activation of the angiogenic switch has been attributed to the synthesis and release of angiogenic factors or reduction of the concentration of endogenous angiogenic inhibitors, including endostatin, angiostatin, and thrombospondin (Ribatti 2009).

Angiogenic factors can be exported from tumor cells, mobilized from the extracellular matrix (Mignatti and Rifkin 1993), or released from the inflammatory cells recruited to the tumor (Ribatti and Crivellato 2009). Tumor angiogenesis is regulated by numerous “classic” pro-angiogenic factors, including fibroblast growth factor-2 (FGF-2), vascular endothelial growth factor (VEGF), and placental growth factor (PIGF). Moreover, evidence has been accumulated that in addition to the “classic” factors, many other “nonclassic factors,” including granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), and erythropoietin (EPO), play an important role (Ribatti et al. 2007b). As a result of the imbalance of angiogenic activators and inhibitors, tumor blood vessels display many structural and functional abnormalities (Ribatti et al. 2007c).

Anti-Angiogenesis

In 1971, Folkman proposed a seminal hypothesis: “prevention of new vessel sprouts from penetrating into an early tumor” will keep the “tiny tumor” in a “dormant” state. Beginning in the 1980s, the pharmaceutical industry began to exploit the field of anti-angiogenesis for creating new therapeutic molecules in angiogenesis-dependent diseases.

In 1993, Ferrara et al. demonstrated that VEGF-blocking antibodies reduced tumor growth and vascular density in animal models (Kim et al. 1993). Bevacizumab (Avastin) was the first angiogenesis inhibitor approved by the Food and Drug administration (FDA) for the treatment of colorectal cancer, in combination with irinotecan, 5-fluorouracil, and leucovorin (Hurwitz et al. 2004). Subsequently, bevacizumab in combination with chemotherapy extended overall survival in metastatic non-small cell lung cancer and advanced cervical cancer (Sandler et al. 2006; Tewari et al. 2014). In multiple randomized phase III clinical trials, bevacizumab conferred a survival benefit only when administered in combination with chemotherapy. Different mechanisms may be involved to explain how anti-angiogenic agents boost the efficacy of chemotherapy (Table 1). Angiogenesis inhibitors enhance the efficacy of certain chemotherapeutics by prolonging their contact time with tumor cells (Cesca et al. 2013).

Several strategies to inhibit the VEGF/VEGF receptor (VEGFR) signaling pathway for the treatment of cancer have been explored. Anti-angiogenic therapy is essentially anti-VEGF/anti-VEGFR therapy (Table 2). In addition to monoclonal antibodies, alternative approaches of inhibiting VEGFRs by using small VEGFR tyrosine kinase inhibitors (TKIs) have been

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<tr>
<th>Table 1</th>
<th>Mechanisms explaining how anti-angiogenic agents boost the efficacy of chemotherapy</th>
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<tr>
<td>Direct effect on tumor cell viability</td>
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<td>Induction of cytotoxicity independently of the vascular effects</td>
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<td>Block of pro-survival signals</td>
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<td>“Normalization” of the tumor microenvironment causing increasing intratumoral delivery of chemotherapy</td>
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<td>Temporary improvement of oxygen and nutrients to tumor cells rendering them more sensitive to cytotoxic agents</td>
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<td>Stimulation of the host immune response</td>
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investigated. TKIs target signaling pathways of VEGFR-1, VEGFR-2, VEGFR-3, and other pro-angiogenic pathways such as the platelet-derived growth factor (PDGF) receptor (PDGFR) and FGF receptor families. TKIs could be more effective than antibody-based therapy that solely target one component of the VEGF/VEGFR pathway. Trials that have combined monoclonal antibodies and TKIs have given rise to an increase of adverse side effects profile.

**Development of Resistance**

The clinical benefits of anti-angiogenic treatments are relatively modest, because the drugs merely slow down tumor progression and prolong survival by only a few more months. When VEGF-targeted therapies are discontinued, the tumor vasculature is rapidly reestablished (Mancuso et al. 2006), suggesting that prolonged use of VEGF-targeted therapy is necessary to achieve maximal therapeutic effect. Continuation of bevacizumab treatment beyond progression was associated with greater benefit in terms of overall survival (Grothey et al. 2008).

Intrinsic resistance is characterized by inefficacy of tumor treatment with anti-angiogenic anti-VEGF, fusion proteins that trap VEGF (Lockhart et al. 2010), or anti-VEGFR TKIs (Batchelor et al. 2010; Gotink and Verheul 2010). Acquired resistance develops as a result of sequential genetic and epigenetic changes that confer to the tumor cells a complex drug-resistant phenotype. Decreased drug uptake, expression of new drug-efflux pumps, drug metabolism, repair of DNA-damage, alterations of cell proliferation, and/or apoptotic mechanisms (Gottesman 2002) are involved in acquired resistance. In acquired resistance, alternative mechanisms lead to activation of angiogenesis even when the target of the drug remains inhibited (Bergers and Hanahan 2008).

**Normalization of Tumor Blood Vessels and Pericyte Coverage**

VEGF inhibition could temporarily restore or normalize the function of tumor-associated vasculature, decreasing vascular permeability in conjunction with restoration of sustained pressure gradients and thereby enhancing systemic delivery of oxygen or perfusion of cytotoxic agents to intratumoral sites (Jain 2001). Abrogation of VEGF signaling increases collagenase IV activity, leading to restoration of normal basement membrane, which generally in tumors has an abnormally thickness.

Moreover, tumor vascular normalization is accompanied by increased pericyte coverage. It has been suggested that pericyte protects the endothelium against drugs (Cooke et al. 2012). In this context, an increase in pericyte coverage as a consequence of angiogenesis inhibition might induce a reduced sensitivity to the drug and acquired resistance.

**Experimental models.** Pericyte coverage promotes resistance through direct support, or paracrine interactions with endothelial cells and tumor vessels covered by pericytes are less sensitive to VEGF blockade (Ribatti et al. 2011). Pericytes can activate compensatory PDGFR-mediated pro-angiogenic signaling under anti-VEGF therapy (Song et al. 2009). Combined treatment or pretreatment with anti-PDGF-B/PDGFR-β reducing pericyte coverage increases the success of anti-VEGF treatment in the mouse RIP1-TAG2 model (Bergers et al. 2003). However, extensive
regression of endothelial cells was not observed in tumors after inhibition of PDGFR-β signaling (Abramsson et al. 2003). After treatment of RIP1-TAG-2 tumors and Lewis lung carcinomas with VEGF-Trap, surviving pericytes may become more tightly associated with endothelial cells or have no apparent association with tumor vessels (Inai et al. 2004). Treatment of RIP1-TAG2 tumors with anti-PDGFR-β antibody reduces pericytes, increases endothelial cell apoptosis, but does not seem to reduce tumor vascular density (Song et al. 2005). Treatment with a DNA oligonucleotide aptamer (AX102) that selectively binds PDGF-B leads to progressive reduction of pericytes in Lewis lung carcinomas (Sennino et al. 2007). Tumors in platelet-depleted mice show diminished pericycle recruitment, resulting in reduced blood vessel density, maturation, and perfusion (Li et al. 2014).

Clinical evidence. VEGFR-2 blockade can lead to the upregulation of angiopoietin-1 (Ang-1) that increases pericyte coverage of the vessels (Winkler et al. 2004). In glioblastoma patients, the Ang-1/Ang-2 ratio correlates with survival (Sie et al. 2009) and vascular normalization, whereas high Ang-2 levels correlate with resistance to anti-VEGF therapy (Batchelor et al. 2010). Blockade of VEGF signaling with the TKI cediranib significantly reduced levels of Ang-2 in the same patients (Batchelor et al. 2010). Ectopic expression of Ang-2 had no effect on vascular permeability, tumor growth, or survival, but it resulted in higher vascular density, with dilated vessels and reduced mural cell coverage (Chae et al. 2010). When combined with anti-VEGFR-2 treatment, Ang-2 destabilized vessels and compromised the survival benefit of VEGFR-2 inhibition by increasing vascular permeability. This suggests that VEGFR-2 inhibition normalized tumor vasculature, whereas ectopic expression of Ang-2 diminished the beneficial effects of VEGFR-2 blockade by inhibiting vessel normalization.

Inhibitors of the VEGF/VEGFR pathway used to treat malignancies of the central nervous system normalize tumor vasculature and decrease tumor interstitial pressure, leading to an improved access of cyto-reductive drugs and radiotherapy efficacy, due to an increased oxygen delivery (Mc Gee et al. 2010). However, these agents may also restore the low permeability characteristics of normal brain microvasculature, counteracting beneficial effects.

Vascular normalization may change the immune response. Inhibitors of VEGF signaling and of prostaglandin E2 suppress Fas ligand expression in tumor endothelial cells, resulting in infiltration of CD8+ T cells (Motz et al. 2014).

Hypoxia

Tumors are hypoxic in spite of high vascularization due to the poor structure and functionality of tumor blood vessels. Hypoxia in tumors develops in the form of chronic hypoxia resulting from long diffusion distances between perfused tumor vessels and loci of acute hypoxia, resulting from transient collapse of tumor vessels. Abnormal tumor vasculature reduces blood flow tumor sites, hindering the delivery of chemotherapeutic drugs and favoring hypoxic microenvironment which, in turn, induced the upregulation of pro-angiogenic factors (Semenza 2014). Moreover, hypoxia mediates immune cell recruitment, and these cells concentrate at the tumor periphery, while in the tumor core, hypoxia provides an aggressive selection for cancer stem cells (CSCs) (Semenza 2014).

Hypoxic areas of tumors are refractory to chemotherapy and radiotherapy and contribute to select tumor cell populations able to escape to metastatic sites and pro-angiogenic CSCs (Blagosklonny 2001, 2004). The improvement in tumor oxygenation seems to last 2–4 days after anti-VEGF treatment (Jain 2013). At later times, increased tumor hypoxia has been reported after bevacizumab treatment (Keunen et al. 2011). VEGF blockade aggravates hypoxia, which in turn upregulates the production of angiogenic factors or increases tumor cell invasiveness (Bergers and Hanahan 2008; Paez-Ribes et al. 2009). Hypoxia-induced expression of surface molecules in tumor endothelial cells directs mobilization of EPCs in growing tumor vessels (Moschetta et al. 2014).
Tumor cells respond to hypoxia by becoming tolerant and modifying their metabolic characteristics to resist low oxygenation (Rapisarda and Melillo 2009), selecting more invasive metastatic clones of cancer cells resistant to anti-angiogenic agents (Semenza 2014). Invasiveness is enhanced through the production of pro-migratory proteins, such as stromal cells derived factor-1 alpha (SDF-1α) and hepatocyte growth factor-scatter factor (HGF-SF) and pro-invasive extracellular matrix proteins (Finger and Giaccia 2010; Semenza 2014). Hypoxia in highly metastatic tumors may cause excessive VEGF production and gene instability in tumor endothelial cells (Taylor et al. 2010).

**Recruitment of Inflammatory Cells and Immature Myeloid Cells**

The most aggressive human cancers, including malignant melanoma, breast carcinoma, and colorectal adenocarcinoma, are associated with the recruitment of various inflammatory cells which are involved in therapy resistance, including macrophages, mast cells (Ribatti 2013), CD11b+/Gr1+ myeloid cells (myeloid-derived suppressor cells, MDSCs) (Shojaei et al. 2007), Tie2+ monocytes (TEMs) (De Palma et al. 2005; 2009), tumor-associated fibroblasts (TAFs) (Raffaghello et al. 2015), and lymphocytes (Ding et al. 2011).

Tumors, refractory to anti-VEGF therapy, display an increased number of MDSCs (Shojaei et al. 2007), and MDSCs derived from these tumors stimulate tumor growth in the presence of anti-VEGF antibodies (Shojaei et al. 2007). TEMs contribute to resistance against anti-VEGF therapy (afiblercept or bevacizumab) and promote glioma cell invasiveness in the xenograft U-87 MG mouse glioma model (Gabrusiewicz et al. 2004). TAFs secrete PDGF-C, and neutralizing antibodies against PDGF-C ameliorate TAF-induced angiogenesis (Crawford et al. 2009). TAFs isolated from tumors, refractory to anti-VEGF therapy, could promote tumor growth of anti-VEGF-sensitive tumors during VEGF-targeted therapy (Crawford and Ferrara 2009). Inhibition of angiogenesis stimulates the infiltration of the subclass of CD4+ T cells (Ding et al. 2011). TAFs-derived exosomes promoted chemoresistance of colon cancer cells upon treatment with 5-fluorouracil or oxaliplatin by increasing the CSC population (Hu et al. 2015). TAFs can induce tamoxifen resistance in MCF7 breast cancer cell line, and metformin can resensitize these cancer cells to tamoxifen (Martinez-Outschoorn et al. 2011). Inflammatory cells secrete other pro-angiogenic factors, including FGF-2, interleukin-8, -17 (IL-8, IL-17) and Ang-2 (Azam et al. 2010; Casanovas et al. 2005; Huang et al. 2010; Chung et al. 2013; Rigamonti et al. 2014). In particular, IL-17 induces the G-CSF-dependent recruitment of CD11b+Gr1+ immature myeloid cells (Chung et al. 2013). IL-8 secreted by bone marrow stromal cells (BMSCs) in multiple myeloma patients contributed to BMSC-induced NF-kB activity, responsible in turn of resistance to bortezomib (Markovina et al. 2010).

GM-CSF stimulates macrophages to produce soluble VEGFR-1 (sVEGFR-1), leading to sequestration of VEGF and subsequent inhibition of angiogenesis, tumor growth, and metastasis (Eubank et al. 2009). Moreover, GM-CSF promotes MDSC survival and renders these cells resistant to sunitinib (Fink et al. 2011).

**Alternative Mechanisms of Tumor Vessel Formation**

Other modes of tumor vascularization may be less sensitive to anti-angiogenic therapies. Intussusceptive microvascular growth (IMG) generates vessels more rapidly with a less metabolic demand as compared to sprouting angiogenesis and is a strategy that tumors can use for rapid adaptation to milieu changes (Ribatti and Djonov 2012). IMG occurs in several tumors, including colon carcinoma, mammary carcinomas, melanoma, B-cell non-Hodgkin’s lymphoma, and glioma (Crivellato et al. 2003; Djonov et al. 2001; Nico et al. 2010; Patan et al. 1996; Ribatti et al. 2005). Treatment of mammary carcinoma allografts with a TKI results in transient reduction in tumor growth rate with decreased tumor
vascularization. After cessation of therapy, the tumor vasculature re-expands prevalently by IMG (Hlushchuk et al. 2008). In this context, anti-angiogenic therapy causes a switch from angiogenesis to IMG, representing an escape mechanism and accounting for the development of resistance. In the course of the so called “vasculogenic mimicry,” blood vessels are generated without the participation of endothelial cells and independent of classical angiogenic factors, including FGF-2 and VEGF (Maniotis et al. 1999). Stimulation with VEGF does not enhance vasculogenic mimicry (van der Schaft et al. 2005), and vasculogenic mimicry might be dependent on CSCs (El Hallani et al. 2010).

Vascular co-option occurs in sites of metastases or in densely vascularized organs. Tumor cells co-opt and grow as cuffs around adjacent vessels (Holash et al. 1999). Vessel co-option has been reported in liver metastases (Vermuelen et al. 2001), non-small cell lung cancer, and lung metastases (Pezzella et al. 1996, 1997). Co-opted vessels initiate an apoptotic cascade mediated by Ang-2 followed by regression of the vessels. Shortly after regression, hypoxic tumor cells expressing VEGF upregulate the angiogenic response (Holash et al. 1999). Treatment of glioma with a monoclonal antibody against VEGFR-2 induces co-option of quiescent cerebral vessels (Kunkel et al. 2001). Similar findings have been reported for cerebral melanoma metastases after treatment with the anti-angiogenic agent ZD6474 (Leenders et al. 2004). More recently, Kuczynski et al. (2016) demonstrated that co-option of liver vessels and not-sprouting angiogenesis drives acquired sorafenib resistance in hepatocellular carcinoma. CSCs secrete VEGF to stimulate tumor angiogenesis; tumor vasculature, in turn, supports CSC self-renewal and maintaining (Alvero et al. 2009). Moreover, CSCs recruit endothelial precursors involved in revascularization and tumor regrowth (Ribatti 2012). Treatment with sunitinib induces elevated plasma levels of SDF-1, potentially contributing to the development of resistance under anti-angiogenic treatment (Ebos et al. 2007). Antibody-mediated blockade of SDF-1, which abrogates EPC-endothelial cell binding can counteract drug resistance (Ceradini et al. 2004).

Orthotopic or subcutaneous injection of glioblastoma stemlike cells in immunocompromised mice generated large anaplastic tumor xenografts, showing a vessel wall formed by human endothelial cells derived from glioblastoma stemlike cells (Ricci-Vitiani et al. 2010). Postnatal vasculogenesis contribute to tumor vascular supply throughout endothelial precursor cells (EPCs), which migrate from the bone marrow and differentiate in the stromal environment of tumors (Asahara et al. 1999).

**Genomic Instability of Tumor Endothelial Cells and Increase of Metastatic Potential**

Until recently, tumor endothelial cells were believed to be genetically stable. However, they are different from normal endothelial cells (Table 3) and may also be heterogeneous among organs or tumor types. The heterogeneity of tumor endothelial cells may be dependent on the tumor microenvironment, tumor stage, or treatment progress.

<table>
<thead>
<tr>
<th>Normal blood vessels</th>
<th>Tumor blood vessels</th>
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<tr>
<td>Hierarchical branching pattern</td>
<td>Unorganized branching pattern</td>
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<td>Pericyte coverage</td>
<td>Tortuous vessels</td>
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<tr>
<td>Polarized</td>
<td>Abnormal basement membrane</td>
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<tr>
<td>Quiescent endothelial cells</td>
<td>Loose of pericytes</td>
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<tr>
<td></td>
<td>Loose of endothelial cell interconnections</td>
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<td></td>
<td>Leaky vessels</td>
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<td>High interstitial fluid pressure (IFP)</td>
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Colorectal cancer endothelial cells overexpress specific transcripts as compared to endothelial cells of the normal colorectal mucosa (St Croix et al. 2000). A distinct gene expression pattern related to extracellular matrix and surface proteins characteristic of proliferating and migrating endothelial cells has been demonstrated in glioma and invasive breast carcinoma (Madden et al. 2004; Parker et al. 2004). Moreover, endothelial cells isolated from various tumors acquired genotype alterations (Hida et al. 2004). Proximity of tumor cells and endothelial cells within the tumor microenvironment may be responsible for the genotype alterations (Gabrusiewicz et al. 2004; Hida and Klagsbrun 2005). Renal carcinoma endothelial cells are resistant to vincristine (Bussolati et al. 2003), while hepatocellular carcinoma endothelial cells are resistant to 5-fluorouracil and adriamycin (Xiang et al. 2009; Akiyama et al. 2012).

Inhibition of the VEGF/VEGFR signaling pathway may exert potential metastasis-promoting effects. Short-term treatment with sunitinib prior to intravenous inoculation of breast and melanoma cells could accelerate metastasis and short survival, despite cessation of treatment (Ebos et al. 2009). Moreover, sunitinib increases metastasis in orthotopic mouse models of breast and colon cancer (Shojaei et al. 2012). Increased invasiveness might result from enhanced expression of VEGF and PlGF or recruitment of EPCs that promote the formation of a pre-metastatic niche (Ebos et al. 2007). Moreover, hypoxia generated by angiogenesis inhibition triggers pathways that make tumors more aggressive and metastatic and less sensitive to anti-angiogenic treatment (Ebos et al. 2009). Finally, VEGF-targeted therapy can allow an epithelial-mesenchymal transition, which could in turn promote increased invasion and metastasis (Lu et al. 2012).

### Conclusion

Anti-angiogenic treatment induces a reactive resistance which is mediated by the HIF/VEGF pathway, allowing both endothelial and cancer cells to resist to therapy (Blagosklonny 2005). Resistance to VEGF pathway inhibitors involves different mechanisms, including normalization of tumor blood vessels, alternative mechanisms of vessel formation, hypoxia, recruitment of inflammatory cells, and immature myeloid cells. All of these mechanisms deserve further investigation both in animal models and in humans to clarify their significance and importance.

VEGF blockade aggravates tumor hypoxia, which upregulates the production of other angiogenic factors in the tumor microenvironment. In this context, targeting VEGF and other pathways implicated in angiogenesis should result in more effective tumor growth inhibition. Moreover, more rational combinations of anti-angiogenic agents based on pharmacokinetic and pharmacodynamic data are needed to overcome resistance, and it is extremely important to determine the optimal duration and scheduling of anti-VEGF agents. The importance of the time interval of the normalization effects of anti-angiogenesis, the so-called window of normalization, has been underlined (Weissleder 2002). Metastatic effects of preclinical anti-angiogenic therapy with an antibody-targeting mouse VEGFR-2 are prevented by concurrent chemotherapy (Paez-Ribes et al. 2015). The identification of specific predictive biomarkers (Table 4) remains an important endpoint even if biomarkers that are predictive of anti-VEGF therapy may be specific to different tissues and tumor subtypes.

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### Table 4 Biomarkers to predict response to angiogenesis inhibitors

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<th>Functional imaging</th>
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<td>[dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI); positron emission tomography (PET)]</td>
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<th>Hypertension</th>
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<tr>
<td>Circulating proteins</td>
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<td>(baseline plasma VEGF concentration; baseline plasma levels or treatment-induced changes in PlGF, soluble VEGFR-2)</td>
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<th>Circulating cells</th>
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<th>Single nucleotide polymorphisms (SNPs)</th>
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<td>(tumor vascularity; VEGF pathway components; markers of tumor cells, endothelial cells, and inflammatory cells)</td>
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Acknowledgment This work was supported by European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n.278570 to DR.

Cross-References

- Anti-Angiogenic Targets: Angiopoietin and Angiopoietin-Receptors
- Anti-Angiogenic Targets: VEGF and VEGF-Receptors
- Biomarkers for Anti-Angiogenic Therapy
- Mechanisms of Anti-Angiogenic Therapy

References


